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Unusual increase in reported cases of Paratyphoid A fever among travellers returning from Cambodia, January to September 2013

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From January to September 2013, a marked increase in notifications of *Salmonella* Paratyphi A infections among travellers returning from Cambodia occurred in France. An investigation revealed 35 cases without a common source: 21 in France, five in Germany, three in the Netherlands, one in Norway, one in the United Kingdom, four in New-Zealand. Data suggest an ongoing event that should trigger further investigation. Travellers to Cambodia should observe preventive measures including good personal hygiene and food handling practices.

In the first eight months of 2013, numbers of *Salmonella* Paratyphi A infections among travellers returning to France from Cambodia increased markedly while several other countries also reported imported cases although to a lesser extent. Concurrently, an increase in *S.* Paratyphi A infections in Phnom Penh, Cambodia, starting in 2011 but with heightened numbers in 2013, was identified. Here we report mainly on the preliminary findings of the investigation of the French cases.

Background

Salmonella enterica serotype Paratyphi A only affects humans and is a cause of paratyphoid fever. Paratyphoid fever can also be caused by *S. enterica* serotypes Paratyphi B d-tartrate non-fermenting or Paratyphi C, and remains a major cause of morbidity in countries with poor sanitation, with an estimated 5.5 million cases occurring annually [1]. In high-income countries, the majority of paratyphoid fever cases are imported from endemic regions. Transmission is faecal-oral, through consumption of contaminated food or water, as well as person-to-person. The incubation period ranges from five to 21 days depending on the inoculum ingested. Acute illness is characterised by fever and malaise; other non-specific symptoms include headaches, abdominal pain, diarrhoea or constipation, maculopapular rash and enlarged spleen. Chronic carriage can occur following acute infection. Reported case-fatality rate is approximately 1% and can be lowered by prompt use of adequate antibiotic therapy [2,3]. Resistance to various drugs including ampicillin, trimethoprim-sulfamethoxazole and quinolones is increasing worldwide and effective treatment requires adapted antibiotic therapy [4,5]. Good personal hygiene and food handling practices are the only preventive measures as there is no effective vaccine against paratyphoid infection [6].

Situation in France

In France, typhoid and paratyphoid fever have been notifiable diseases since 1903. In addition to mandatory reporting, clinical laboratories forward the isolates to the National Reference Centre for *Salmonella* (NRC) at the Pasteur Institute in Paris on a voluntary basis. Between 2003 and 2012, 272 cases of paratyphoid A fever were reported (annual range: 18–36), including only seven cases among travellers returning from Cambodia.

On 22 August 2013, the NRC notified the French National Institute for Public Health Surveillance (InVS) in Paris, about an unusual increase in the number of cases of paratyphoid A fever among travellers returning from Cambodia: from 1 January to 22 August 2013, 14 cases had been identified at the NRC. We initiated

an investigation to determine the magnitude of the event and to identify potential sources of infection.

Investigation of the event and results

We defined a case as culture-confirmed *S.* Paratyphi A infection diagnosed in 2013 in a person who reported a travel history to Cambodia in the month prior to symptom onset. We merged data from both the NRC and the notifiable diseases surveillance system. Identified persons were contacted by phone, and demographics, clinical data, exposure history and details about their journey in Cambodia were collected using a specifically designed questionnaire.

As *S.* Paratyphi A is known to be a highly clonal organism that pulsed-field gel electrophoresis (PFGE) or multilocus sequence typing (MLST) techniques can hardly discriminate, the NRC focused microbiological characterisation on antimicrobial susceptibility testing and attempted to discriminate isolates by using sequencing of the Clustered Regularly Interspaced Palindromic Repeats (CRISPR) contents, as previously described [7,8]. We carried out antimicrobial susceptibility testing on all available *S.* Paratyphi A isolates by using the disk diffusion method, with a panel of 32 antimicrobial drugs (Bio-Rad, Marnes-La-Coquette, France). We determined the minimum inhibitory concentration (MIC) of ciprofloxacin, nalidixic acid and azithromycin using Etests (bioMérieux, Marcy l'Etoile, France), as previously described [9]. The results were then interpreted using the breakpoints of the Antibiogram Committee of the French Society for Microbiology (CA-SFM).

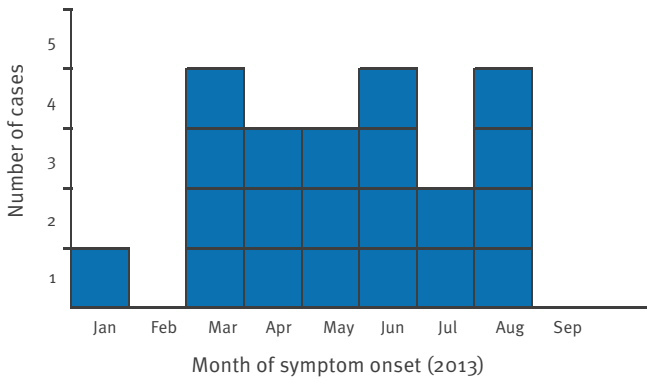
On 28 August 2013, the InVS sent out an alert through the European Epidemic Intelligence Information System for Food- and Waterborne Diseases (EPIS-FWD) of the European Centre for Disease Prevention and Control (ECDC) to inform other European Union/European Economic Area (EU/EEA) Member States and associated national public health institutes about the event and to query about any recent increase in their reported cases of paratyphoid A fever with a travel history to Cambodia. Countries that responded and reported cases with a travel history to Cambodia in 2013 were contacted by ECDC to obtain additional information. Moreover, ECDC used the European Surveillance System (TESSy) to compare the number of cases with a travel history to Cambodia reported in the EU/EEA in 2013 with previous years. On 28 August, when available information suggested a multinational event, the French health authorities sent out an Early Warning Response System (EWRS) message, and on 4 September, ECDC posted a rapid risk assessment on its website to alert a wider audience about the event [10].

Cases notified in France

In France, from 1 January to 20 September 2013, 21 cases of paratyphoid A fever among persons with a travel history to Cambodia in the month prior to symptom onset were reported. This represents a significant increase in the reported number of cases since only seven cases were reported between 2003 and 2012: two in 2003, three in 2004, one in 2005 and one in 2012. Dates of symptom onset ranged from 30 January to 31 August 2013 (Figure) and dates for reported travel history to Cambodia ranged from 23 January to 27 August.

Figure

Cases of paratyphoid A fever among travellers returning from Cambodia by month of symptom onset, France, 2013 (n=21)



Median age of infected persons was 40 years (range: 4–65 years), 67% were female and 86% were hospitalised. Clinical data were available for 17/21 cases. Among patients for whom medical information was available, all presented with fever, 16/17 complained of asthenia, 13/17 had chills, 12/17 had diarrhoea, 11/17 had headaches, 9/17 had abdominal pain and 4/17 had nausea or vomiting. Median length of hospitalisation was five days (range: 1–13). All patients fully recovered. Median length of stay in Cambodia was 19 days (range: 4–81 days). Six persons experienced symptoms during their trip in Cambodia and 13 had symptom onset after their return home. For the six persons who had symptoms while in Cambodia, none sought medical attention during their trip, and median lag between arrival and symptom onset was 34 days (range: 11–61). For the 13 persons who had symptoms after their departure from Cambodia, median lag between departure and symptom onset was 12 days (range: 2–26).

One person continued to shed *S.* Paratyphi A in his urine four months after diagnosis, which caused secondary transmission to a household member who presented with bacteraemia. Illnesses occurred in tourists visiting Cambodia and travellers visiting relatives. Interviews did not identify any common exposure (such as hotel, restaurant, airline company or touristic site) that could explain all cases; 1/17 interviewee only visited the city of Phnom Penh, 2/17 interviewees visited Phnom Penh and Siem Reap areas only, and 14/17 visited at least three different cities. Overall, all 17 interviewees visited Phnom Penh area, 12/17 visited Siem

Reap area, 11/17 visited Sihanoukville area whereas other geographic areas were visited by less than 4/17 interviewees. No common exposure or common activity was identified in Phnom Penh. Fourteen of the 21 cases had solely travelled to Cambodia, whereas the remaining seven cases also reported brief travel to Thailand, Vietnam, Myanmar or China prior to symptom onset. The majority of interviewees reported consumption of at-risk food items during their trip: 15/17 ate raw vegetables or drank raw fruit juices, 16/17 had drinks with ice, and 15/17 were not vaccinated against typhoid fever.

S. Paratyphi A isolates were available at the NRC for 18/21 cases with a travel history to Cambodia, which accounted for 45% of *S.* Paratyphi A isolates received at the NRC as of 20 September 2013. All isolates were fully susceptible to a panel of 32 antibiotics systematically tested at the NRC, including ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones and azithromycin. A unique CRISPR profile was found in all 18 isolates and belonged to the dominant profile found in the NRC CRISPR database (36/48 *S.* Paratyphi A isolates).

Cases notified in other countries

Following the EPIS-FWD alert sent out by the InVS on 28 August, Germany, the Netherlands, Norway, the United Kingdom (UK) and New Zealand reported cases of *S.* Paratyphi A infection identified in 2013 among travellers returning from Cambodia. Since 1 January 2013, 35 cases of paratyphoid A fever have been reported among travellers returning from Cambodia including the 21 cases in France, five cases in Germany, three cases in the Netherlands, one case in Norway, one case in the UK, and four cases in New-Zealand. For the EU/EEA countries this represents a significant increase since only three imported cases from Cambodia were reported in the EU/EEA in 2012 (two by Germany, one by France). No reliable data were available for 2010 and 2011. In addition to the 18 isolates tested in France, five additional isolates from other countries were available and were fully susceptible to all tested antibiotics.

Austria, Czech Republic, Cyprus, Denmark, Estonia, Finland, Greece, Hungary, Ireland, Latvia, Lithuania, Malta, Portugal, Slovenia and Sweden reported having no cases in 2013 to date.

The Table summarises the number of reported cases of paratyphoid A fever among travellers returning from Cambodia in 2013, in the EU/EEA and in New Zealand.

Discussion

A marked increase in imported cases of *S.* Paratyphi A infections from Cambodia to France occurred from January to September 2013. Other EU/EEA countries such as Germany, the Netherlands, Norway, the UK, as well as New Zealand also reported cases, although numbers might not differ from the expected baseline range. Occurrence of cases over several months among persons with travel history in different Cambodian geographic areas and without any common exposure identified despite in depth interviews suggests that sources of contamination are persistent and potentially multiple. All 17 French interviewees have visited Phnom Penh; however, Phnom Penh is the primary point of entry for travellers in Cambodia. Available information from a referral hospital in Phnom Penh reported in this issue of *Eurosurveillance* by Vlieghe et al. shows a recent increase in *S.* Paratyphi A infections since March 2013 in residents of Cambodia and particularly in the Phnom Penh area [11]. This study suggests that the rate of infection is higher in Phnom Penh compared to other regions of Cambodia. However, the study site is located in Phnom Penh and therefore, recruitment bias might have affected this finding. Further investigation should be conducted to determine affected areas and to identify sources of contamination of residents of Cambodia.

Table

Cases of paratyphoid A fever among travellers returning from Cambodia, reported in the EU/EEA and in New Zealand, 2013 (n=35)

Country	Number of cases of paratyphoid A fever	Period of reporting (2013)	Antibiotic resistance profile
France	21	Jan–Aug	18 isolates available, susceptible to all tested antibiotics
Germany	5	Jan–May	1 isolate available, susceptible to all tested antibiotics
The Netherlands	3	Mar–Apr	All 3 isolates susceptible to all tested antibiotics
Norway	1	Apr	Isolate susceptible to all tested antibiotics
United Kingdom	1	Apr	No information available
New Zealand	4	May–Aug	1 isolate available, susceptible to all tested antibiotics except streptomycin
Total	**35**	**Jan–Aug**	**23 isolates susceptible to all tested antibiotics**

EU/EEA: European Union/European Economic Area.

According to the Cambodian Ministry of Tourism data, 121,175 French tourists travelled to Cambodia in 2012, versus 110,182 British, 72,537 Germans, 24,559 Dutch, 8,251 Norwegians, and 19,044 New Zealanders [12]. Assuming that the number of travellers to Cambodia by country of residence in 2013 does not significantly differ from the 2012 data (available information suggests similar proportions up to May 2013), these statistics suggest that the large number of French tourists visiting Cambodia could have contributed to the predominance of French nationals among the imported cases. Taking into account the number of travellers by country, the proportions of French, British, German, Dutch, Norwegians and New Zealanders among the cases are 1 per 5,770 French travellers, 1 per 110,182 British travellers, 1 per 14,507 German travellers, 1 per 8,186 Dutch travellers, 1 per 8,251 Norwegian travellers, and 1 per 4,761 New Zealander travellers. The observed differences between countries might reflect differences in travel routes among international travellers, as well as in food habits during travel and in surveillance systems between European countries.

The strains' full susceptibility profile to all antibiotics tested appears common in southeast Asia whereas the spread of *S.* Paratyphi A strains resistant to quinolones has been described in the Indian subcontinent [13]. CRIPSR typing results suggest that CRISPR typing was not sufficiently powerful in discriminating isolates. Further subtyping, i.e. PFGE analysis with two enzymes, of available isolates is ongoing.

Additional cases might occur if the source(s) of contamination persists. However, spread within the EU/EEA through secondary human-to-human transmission is expected to be limited: only one case of secondary transmission among household members has been documented in France so far. Clinicians in travel clinics and in infectious diseases hospitals should be alerted about the increase in the number of *S.* Paratyphi A infections among travellers returning from Cambodia. Advices about preventive measures, including personal hygiene and food handling practices, should be reinforced for travellers to Cambodia before their departure. As for other low and middle income countries, travellers to Cambodia should observe these measures and should seek medical attention as soon as possible should they present symptoms during their trip or after they returned in their country of residence. Although there is no efficient vaccine available against paratyphoid fever, travellers to Cambodia should consider typhoid fever vaccine prior to their trip, unlike the majority of interviewed travellers described in this report, as data from Vlieghe et al. also strongly suggest an ongoing increase in typhoid fever cases in Phnom Penh area [11] .

Finally, whenever possible, travellers returning from Cambodia diagnosed with *S.* Paratyphi A infection should be interviewed by public health authorities; their travel route in Cambodia should be detailed and information should be shared with other countries and Cambodian health authorities to help shed light on any potential source of infection.

Conflict of interest

None declared.

Authors' contributions

Mathieu Tourdjman: led the investigation in France, conducted interviews, analysed data and wrote the manuscript.
Simon Le Hello, Laetitia Fabre, François-Xavier Weill: led microbiological investigation in France and revised the article for intellectual content.
Céline Gossner: coordinated EU investigation, including rapid risk assessment and revised the article for intellectual content.
Gilles Delmas, Sarah Tubiana: conducted interviews and revised the article for intellectual content.
Alexandra Kerléguer, Arnaud Tarantola: reviewed paratyphoid A fever data available from the Pasteur Institute in Cambodia, including microbiological data, and revised the article for intellectual content.
Angelika Fruth: led investigation in Germany and revised the article for intellectual content.
Ingrid Friesema: led investigation in The Netherlands and revised the article for intellectual content.
Lin Thorstensen Brandal: led investigation in Norway and revised the article for intellectual content.
Joanne Lawrence, Ian Fisher: led investigation in The UK and revised the article for intellectual content.
Muriel Dufour: led investigation in New Zealand and revised the article for intellectual content.
Henriette de Valk: supervised the investigation in France and revised the article for intellectual content.

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Increase in *Salmonella enterica* serovar Paratyphi A infections in Phnom Penh, Cambodia, January 2011 to August 2013

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We report an increased number of *Salmonella enterica* Paratyphi A infections in adults in Cambodia. Between January 2011 and August 2013, 71 *S.* Paratyphi A isolates were recovered from blood cultures, representing a 44-fold increase compared to July 2007 to December 2010, while monthly numbers of cultures did not change. Infections with *S.* Typhi increased two-fold in the same period. Most cases came from the capital Phnom Penh. These findings warrant epidemiological investigation to support public health measures.

Between 1 January 2011 and 31 August 2013, there has been a marked increase of *Salmonella enterica* serovar Paratyphi A cases diagnosed from blood cultures in Cambodian citizens, particularly in 2013, and this was reflected in an increased recovery of this pathogen from European travellers returning from Cambodia between January and August 2013 [1]. Here, we report preliminary surveillance data from Cambodia.

Background

S. enterica is an important pathogen in many low and middle income countries [2]. The serovars *S.* Typhi and Paratyphi cause enteric fever (i.e. typhoid and paratyphoid fever respectively), and are particularly prevalent in south and southeast Asia. Treatment has become challenging because of emerging antibiotic resistance to first-line antibiotics such as chloramphenicol, ampicillin, sulphamethoxazole-trimethoprim (SMX-TMP) and more recently fluoroquinolones [3]. Over the past two decades, *S.* Paratyphi A has become increasingly prevalent in Asia, causing between 15% (Pakistan, Indonesia) and 64% (southeast China) of enteric fever cases in these countries [4]. Typhoid and paratyphoid fever are also endemic in Cambodia [5-7]. Nationwide surveillance of incidence and antibiotic resistance patterns is, however, largely lacking due to the country's very limited microbiology laboratory infrastructure [8]. Since July 2007, the Cambodian non-governmental (NGO) hospital Sihanouk Hospital Centre of HOPE (SHCH) in Phnom Penh, and the Institute of Tropical Medicine, Antwerp, Belgium co-organise surveillance of bloodstream infections in Cambodian adults attending SHCH. The 30-bed adults' hospital and its associated clinics provide over 135,000 outpatient visits and about 1,000 hospitalisations per year of patients from across Cambodia. Of 6,881 blood cultures drawn between July 2007 and December 2010, we recorded two patients infected with *S.* Paratyphi A [9].

Laboratory procedures for surveillance of bloodstream infections

From all patients presenting at SHCH with signs of the Systemic Inflammatory Response Syndrome (SIRS) [10], 2 x 10 ml of venous blood are sampled by separate venipuncture with registration of demographic and clinical data (i.e. sex, age, province and district of residence, co-morbidity, prior use of antibiotics, type and duration of symptoms, presumed focus of infection, hospitalisation status). Blood is cultured in BacT/ALERT culture bottles (bioMérieux, Marcy l'Etoile, France) which are incubated at 35°C for seven days and checked once daily for growth by visual inspection of the chromogenic growth indicator. When positive, blood cultures are Gram stained and -in case Gram-negative rods are present- inoculated on MacConkey agar and 5% sheep blood agar (BIO-RAD, Hercules, United States). In addition, blood culture vials with no indication of growth after three days of incubation are subcultured on sheep blood agar. As part of standard patient care, isolates are identified by conventional methods and assessed for antibiotic susceptibility by disk diffusion (Neo-SensitabsTM, Rosco Diagnostica, Taastrup, Denmark) according to the Clinical Laboratory Standards Institute [11]. Serotyping is carried out by slide agglutination with commercial antisera according to the Kauffmann-White scheme [12].

In this report, 'paratyphoid fever' and 'typhoid fever' cases were defined as a patient with culture-confirmed bloodstream infection due to *S.* Paratyphi A or *S.* Typhi respectively. Patients with blood cultures that did not

Figure 1

Salmonella Paratyphi A and *Salmonella* Typhi infections diagnosed at Sihanouk Hospital Centre of HOPE, Phnom Penh, Cambodia, January 2011–August 2013 (n=102)

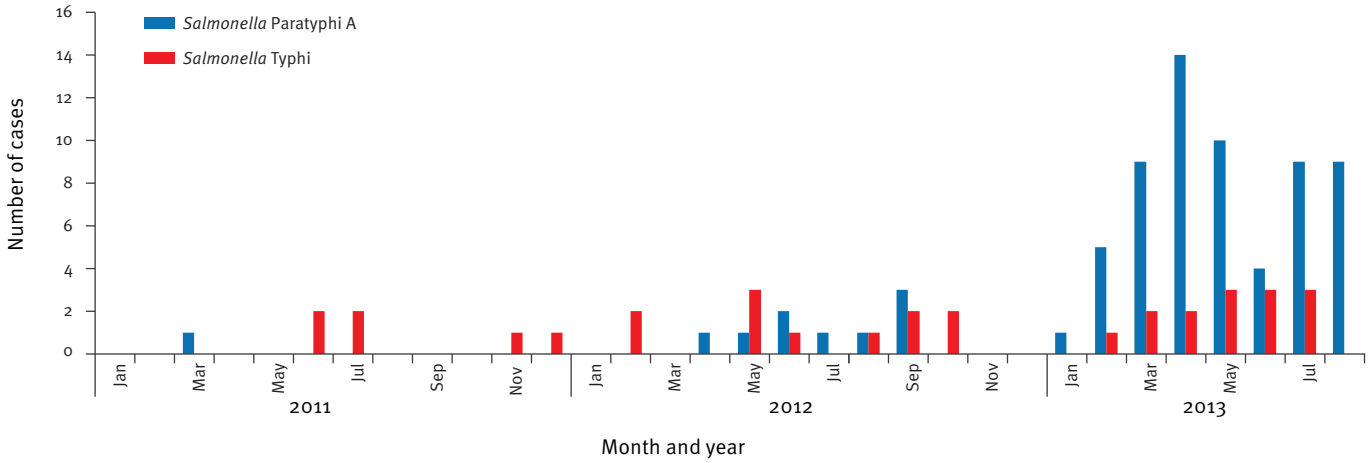


Figure 2

Geographical origin of *Salmonella* Paratyphi A cases diagnosed at Sihanouk Hospital Centre of HOPE, Phnom Penh, Cambodia, January 2011–August 2013 (n=71)

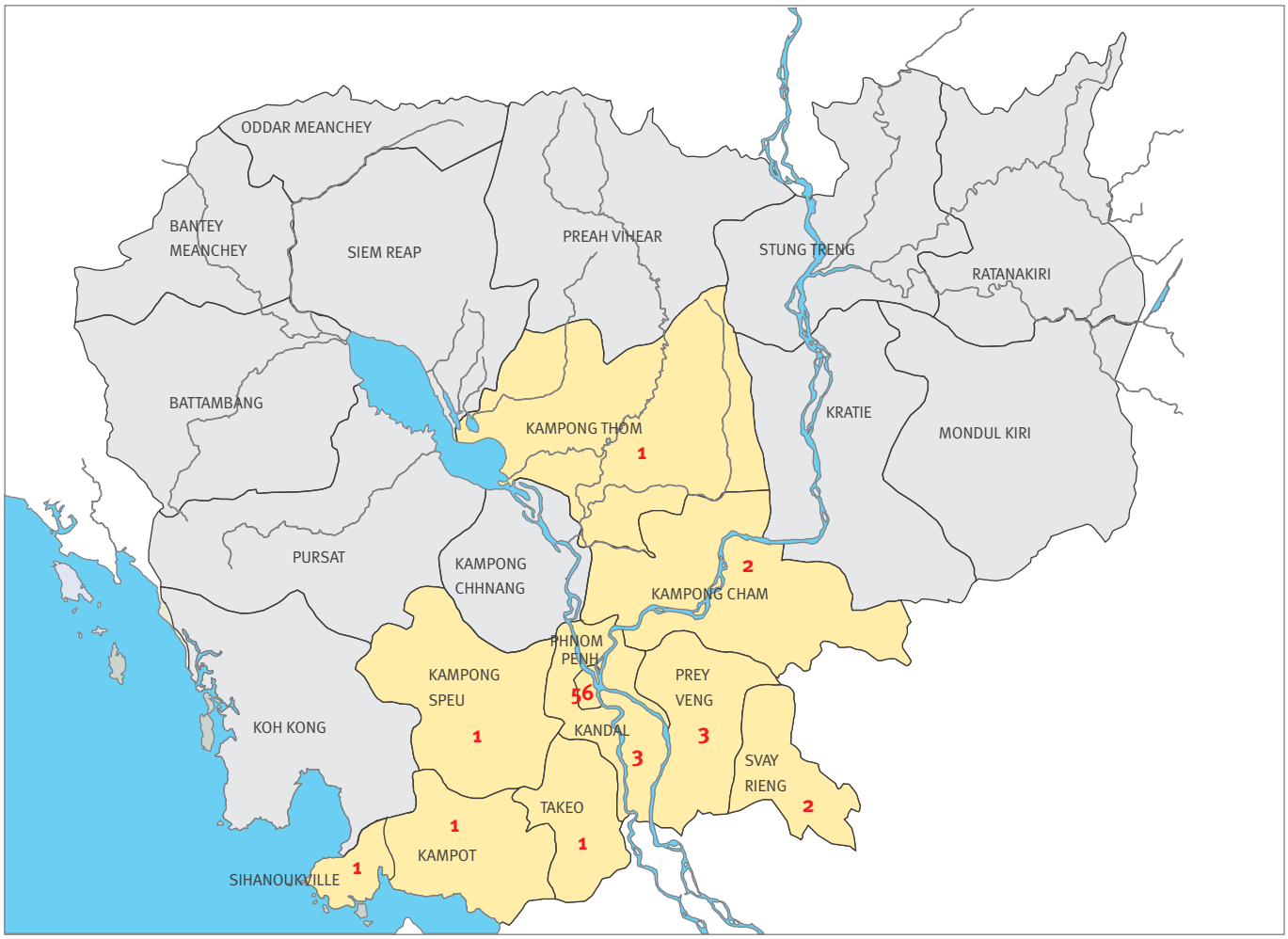
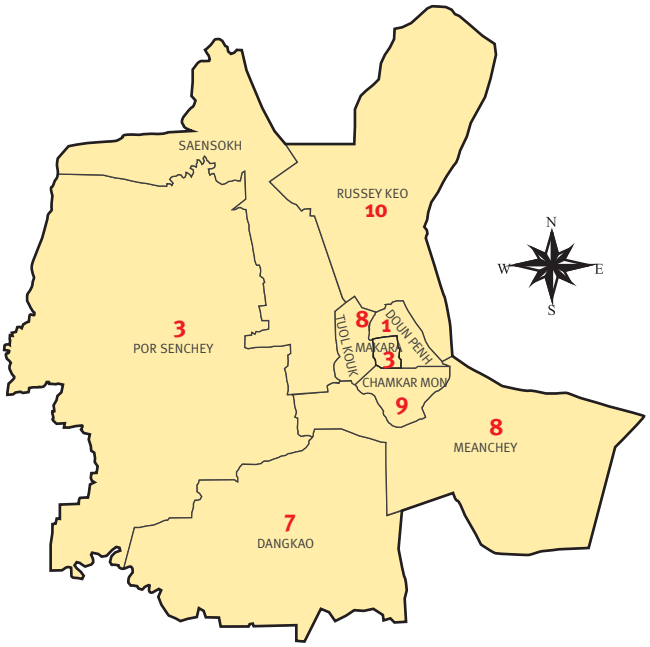


Figure 3

Distribution of *Salmonella* Paratyphi A cases living in Phnom Penh, diagnosed at Sihanouk Hospital Centre of HOPE, Phnom Penh, Cambodia, January 2011–August 2013 (n=56[a])



[a] District unknown for seven cases.

grow after complete work-up or that revealed pathogens other than '*S.* Typhi/Paratyphi A' were not considered 'cases' for the purpose of this investigation.

Ethical approval was granted by the review boards at Institute of Tropical Medicine, Antwerp, the University Hospital Antwerp and the National Ethics Committee for Health Research, Phnom Penh, Cambodia respectively.

Surveillance of blood cultures, 1 January 2011 to 31 August 2013

Between 1 January 2011 and 31 August 2013, 102 cases of enteric fever were diagnosed in Cambodian citizens i.e. 71 with paratyphoid fever and 31 with typhoid fever. Seven cases were recorded in 2011, 20 in 2012 and 75 in the first eight months of 2013. As shown in Figure 1, paratyphoid fever cases were observed more frequently from April 2012 and numbers increased further from March 2013 onwards. Typhoid fever cases increased as well but to a lesser extent.

Forty-seven per cent (i.e. 35 of 71 (49.3%) paratyphoid cases and 13/31 (41.9%) typhoid cases) were female, with a median age of 24 years (range 7–54 years); ages of paratyphoid and typhoid cases were not significantly different.

Out of 71 paratyphoid fever cases, 56 lived in the greater Phnom Penh area (Figure 2), particularly in the following districts: Russey Keo (n=10), Chamkar Mon (n=9), Tuol Kouk (n=8), Mean Chey (n=8), Dangkao (n=7), Prampir Makara (n=3), Por Senchey (n=3), Doun Penh (n=1) (Figure 3). Typhoid fever cases were more dispersed: 19 of 31 were from Phnom Penh, but distributed in small numbers among a large number of districts.

Preliminary susceptibility data based on laboratory files revealed that only 1 of 71 (1.4%) *S.* Paratyphi A isolates was resistant to ampicillin, none to sulphamethoxazole-trimethoprim (SMX-TMP) and three (4.2%) displayed nalidixic acid resistance.

In contrast, 14 out of 31 *S.* Typhi isolates were ampicillin resistant, 11 were SMX-TMP resistant and all but two isolates were nalidixic acid resistant. Six isolates displayed high level ciprofloxacin resistance. Results of minimal inhibitory concentrations for ciprofloxacin are pending.

Empiric treatment included most often ceftriaxone followed by oral ciprofloxacin. So far, there was neither in-hospital mortality, nor relapse recorded.

Discussion and conclusion

Between January 2011 and August 2013, and particularly in the first eight months of 2013, we noted a remarkable increase in paratyphoid fever mainly among young adults treated in our hospital and clinics in Phnom Penh. Compared to the recovery of only two *S.* Paratyphi A isolates during the surveillance period 2007-2010 [9], this represents a 44-fold increase, while the monthly rate of blood cultures remained constant around 150-200. In June we observed a temporary drop in cases, for which we do not have a conclusive explanation, although it may be possible that cases coincidentally visited other healthcare facilities (mostly without culture facilities) within the metropolitan area.

Although it was not possible in the present setting to calculate population-based incidence data, the clustering in time and place of the recent *S.* Paratyphi A cases is of concern and suggests the implication of a common and persistent source. This could be either a continuing disseminating source (i.e. water) or a continuing point source such as a food vehicle. Consumption of food from street vendors has been found an independent risk factor for acquisition of paratyphoid fever in other Asian countries e.g. Nepal and Indonesia [13,14] . Of note, we observed also a two-fold increase of infections due to *S.* Typhi. Given the fact that predominantly adolescents and adults visit our hospital, more data on the possible spread of paratyphoid fever among Cambodian children are certainly needed.

Our findings coincide with the observation of increased numbers of *S.* Paratyphi A infection among European travellers from France, Germany, the Netherlands, New Zealand, Norway and the United Kingdom returning from Cambodia as communicated in a rapid risk

assessment by the European Centre for Disease Prevention and Control (ECDC) on 4 September [1]. Cases from France are described in detail by Tourdjman and colleagues in this issue of *Eurosurveillance* [15].

Of note, most *S.* Paratyphi A isolated in Cambodia between 2011 and 2013 and from travellers in 2013, displayed low resistance levels for most commonly used antibiotics in contrast with *S.* Typhi and other Gram-negative pathogens in Cambodia studied between 2007 and 2010 [7]. To enable a more refined resistance description, we plan further batch-tested determination of the minimal inhibitory concentrations for ciprofloxacin, nalidixic acid and azithromycin amongst other antibiotics.

Further in-depth epidemiological research and a comparative analysis of clonal relationships between the Cambodian and European isolates are warranted to identify the source of the outbreak. Both findings, those in Cambodian citizens and European travellers, suggest that the 'hotspot' of this outbreak may be located in Phnom Penh, home to over a million inhabitants and a major gateway for visitors to the country.

Our findings were shared with the Ministry of Health of Cambodia, to allow the initiation of in-depth epidemiological investigations in order to organise the required public health measures. Cambodia, like many other low- and middle-income countries, is still building up its microbiological diagnostic capacity; across the country, less than 15 microbiology laboratories are in function [8]. In these settings, even small-scale clinical laboratories, such as the one in our hospital, may play an important role as 'sentinel' for emerging pathogens and resistance patterns.

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Conflict of interest

None declared.

Authors' contributions

Conceived and designed the study: JJ, EV, BDS.
Collected microbiological data: CK,DS,BDS.
Collected clinical and epidemiological data: TP, CHV, KL.
Analysed data: EV, BDS, TP, JJ, JvG.
Wrote the paper: EV, JJ, JvG, TP,ST.

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Taking stock of the first 133 MERS coronavirus cases globally – Is the epidemic changing?

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Since June 2012, 133 Middle East respiratory syndrome coronavirus (MERS-CoV) cases have been identified in nine countries. Two time periods in 2013 were compared to identify changes in the epidemiology. The case-fatality risk (CFR) is 45% and is decreasing. Men have a higher CFR (52%) and are over-represented among cases. Thirteen out of 14 known primary cases died. The sex-ratio is more balanced in the latter period. Nosocomial transmission was implied in 26% of the cases.

Since the emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) in June 2012, 133 cases have been identified so far. All primary cases were connected to the Arabian Peninsula and nearly half of the cases died. Even though over a year has passed since the emergence of the first case, many questions on the origin and transmission patterns of the disease remain. The imminent start of the Hajj, the Muslim pilgrimage to Mecca in Saudi Arabia, in early October, is reason to review the epidemiological characteristics of the first 133 cases of MERS reported to the World Health Organization (WHO) as of 25 September 2013.

Background

The index case of the newly described MERS-CoV was detected in the Kingdom of Saudi Arabia (SA) in June 2012 [1]. Hereafter, cases and clusters of nosocomial or familial transmission were detected in nine countries in the Middle East [2-4], four in Europe [5-12] and one in Africa [13]. The virus was isolated from several cases and full sequence data are available through GenBank [14].

The reservoir and hosts of the MERS-CoV are still unknown, although virus RNA was possibly detected from bat faeces collected in the vicinity of the index case [15]. The virus belongs to the lineage C of the genus of beta coronaviruses, which are genetically similar to various coronaviruses detected in bats in Africa and Europe [16,17]. Two studies suggest dromedary camels in Oman, the Canary Islands and Egypt may have been infected with the virus or a MERS-CoV-like virus in the past. However, human cases have not been detected in these areas [18,19].

Epidemiological findings as of 25 September 2013

Data collection

This paper reviews the epidemiological characteristics of the first 133 cases of MERS, reported applying the WHO case definition, as available on the Ministry of Health (MoH) of affected countries and WHO websites [20-24] and is based on [25]. Basic demographic data (age, sex and comorbidities) on disease severity in terms of treatment level (outpatient, hospitalised, admitted to intensive care) and information on outcomes are usually available through MoH websites and WHO Disease Outbreak News. Further details were collected from peer-reviewed publications and through direct communication with the SA Ministry of Health.

All data were collected contemporaneously into a line listing on MS Excel 2010 and subsequently cross-checked with existing peer-reviewed publications on cases or clusters.

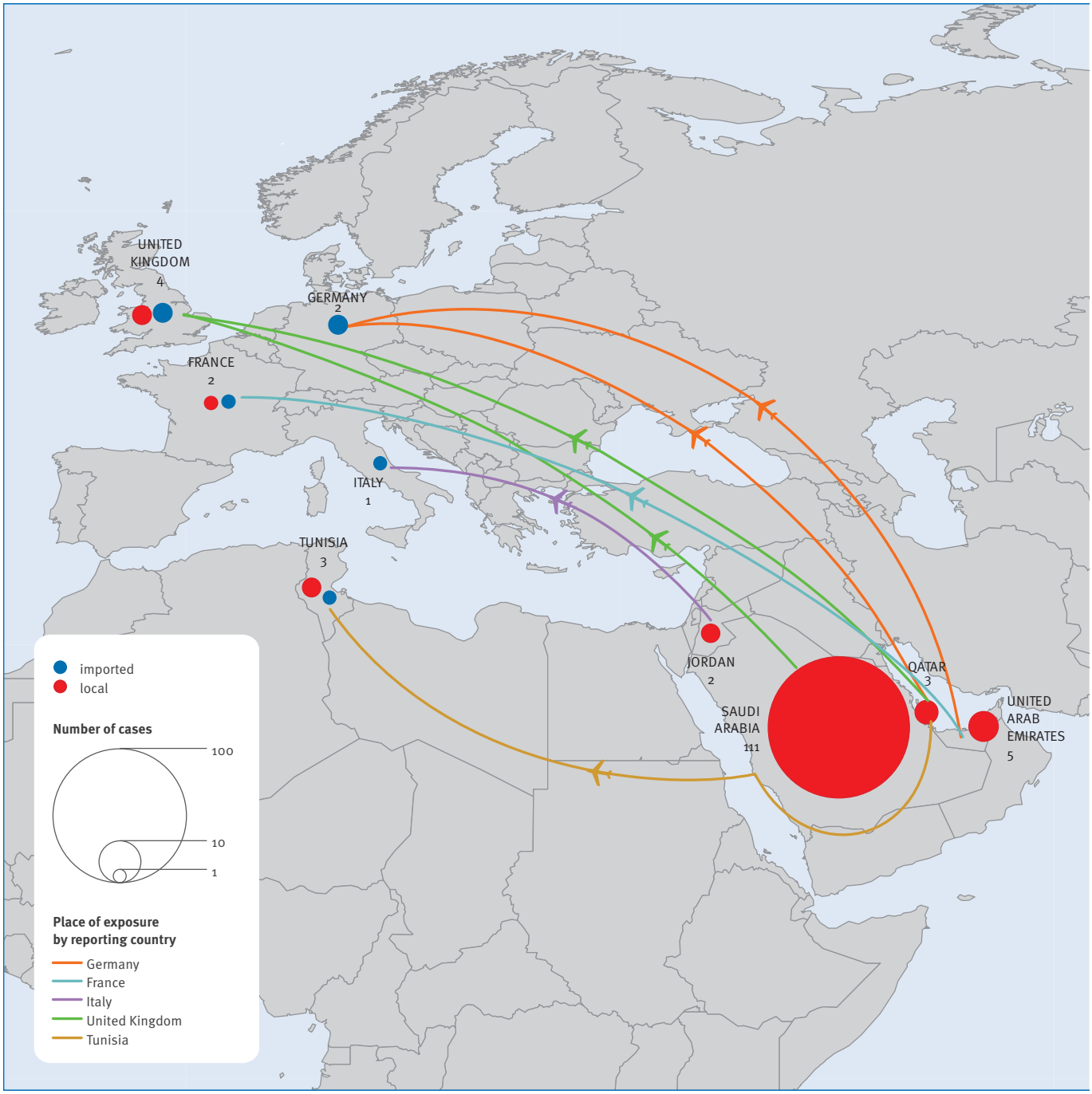
For female to male ratio, case-fatality risk (CFR) and admission to an intensive care unit (ICU), we compared two time periods of transmission in 2013: March to May versus June to September, thus excluding the rather sporadic cases in 2012 and early 2013.

Cases retrieved

Between 30 March 2012 and 25 September 2013, 133 confirmed cases of MERS-CoV infections have been reported by nine countries (Figure 1). All cases have an epidemiological link to Jordan, KSA, United Arab Emirates (UAE) or Qatar. Cases detected in Europe [5-9] are linked to patients medically evacuated or seeking care in Europe.

Figure 1

MERS coronavirus cases by reporting country, as of 25 September 2013 (n=133)



Source: [25].

MERS: Middle East respiratory syndrome.

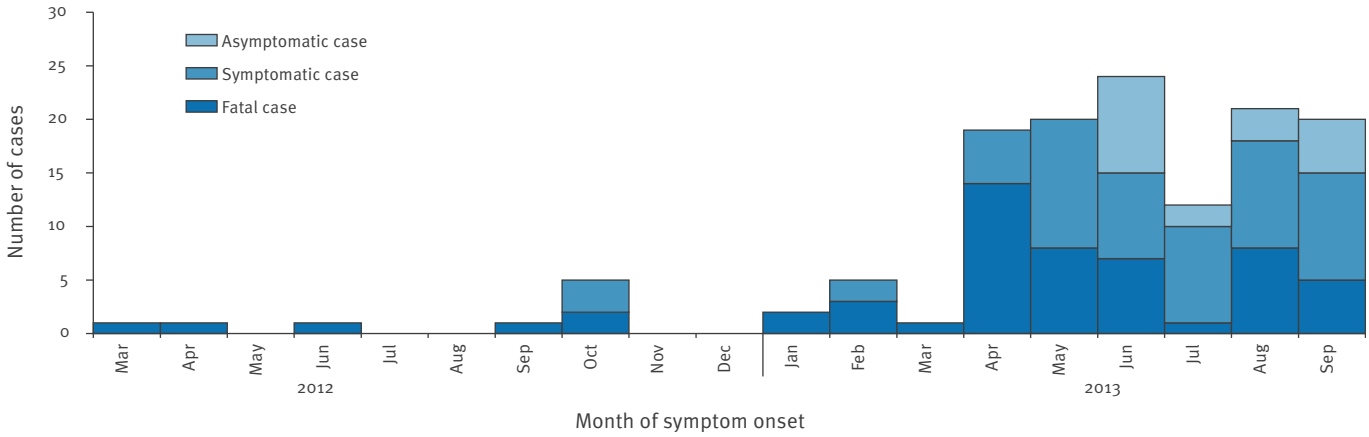
The temporal distribution of cases suggests ongoing transmission (Figure 2).

Since June 2013, 18 asymptomatic or mildly symptomatic cases have been reported. All were without any symptom or very mild with one episode of fever with or without myalgia and chills. In SA, 16 asymptomatic cases were detected during screening of all contacts of diagnosed cases and were included if positive for two specific gene targets (upE and ORF1a) on polymerase chain reaction (PCR). The remaining two asymptomatic cases were detected in UAE.

The majority of reported cases are adult men and very few children or adolescents have been diagnosed with MERS-CoV infection (Table). The female to male ratio

Figure 2

Distribution of confirmed MERS coronavirus cases by month of symptom onset[a], March 2012–25 September 2013 (n=133)



MERS: Middle East respiratory syndrome.

[a] Where month of onset was not available, month of reporting was used.

of cases is 0.67 overall. However, it increased in 2013 from 0.33 in March to May, to 1.08 in June to September.

We identified 14 clusters of 2-34 cases, where the primary cases were identified or suspected. However, data quality on the clusters is weak. All of the known 14 primary cases in clusters were adult men (24-83 years old) who were most likely exposed on the Arabian Peninsula. Of 129 cases with available information on transmission, 33 (26%) were possible nosocomial transmissions, 15 of these cases were healthcare workers (HCW). Seventeen of the 23 cases reported as HCW were female.

Of all reported 133 cases, 60 (45%) cases were admitted to intensive care (ICU). In comparison, between March and May 2013, 25 of 40 cases (63%) were admitted to ICU, while from June to September 2013, 25 of 77 cases (33%) were admitted to intensive care.

The overall CFR among the 133 cases is 45% on 25 September 2013. Among symptomatic cases the CFR decreased from 23 of 40 cases (58%) in March to May to 21 of 77 (27%) in June to September.

Men have a higher CFR compared with females (52 versus 24%) (Table). Among the known primary cases in clusters with available information on outcomes, the CFR is 93% (13/14).

Seventy-three per cent of the 55 fatalities had at least one comorbidity reported compared to 41% of 73 surviving cases. All deaths have been reported among adults except one in a two-year-old child.

Discussion

MERS-CoV cases exposed in the Arabian Peninsula were identified in the European Union and in Tunisia mainly while seeking medical care. This has resulted in secondary transmission. The majority of travels from the Arabian Peninsula however, are destined to Asian countries which suggests that the risk of introductions exists also in Asia [26]. No cases have been reported there to date, despite enhanced surveillance in some countries. It is noteworthy that no infected cases have been detected outside the Arabian Peninsula since May 2013. The striking overrepresentation of men among cases in the first months balanced over time. This can be partly explained by the higher proportion of female HCW among recently reported nosocomial transmissions. In a similar fashion, the median age of cases has decreased.

Our assessment of the severity of the disease and outcomes is based on available data at the time of the reporting from the country and may result in under ascertainment of severe outcomes. At the same time, the proportion of cases admitted to intensive care and the CFR has decreased over time, which may be a reflection of enhanced surveillance activities.

'Superspreading' events or cases were interpreted as a key cause for the progression of the severe acute respiratory syndrome (SARS) outbreak in 2003 [27]. The large nosocomial cluster of MERS in Al Hasa, Saudi Arabia, involving up to 23 cases has some similarities with such events. It could have been caused by multiple zoonotic or human introductions in the community or inconsistencies in applying appropriate

Table

Distribution of confirmed MERS coronavirus cases and fatalities by age and sex, March 2012–25 September 2013 (n=128)[a]

Age range (years)	Female		Male		Total number of cases
	Dead	Total	Dead	Total	
0-9	0	3	1	1	4
10-19	0	4	0	3	7
20-29	0	2	4	9	11
30-39	0	7	5	11	18
40-49	2	9	3	13	22
50-59	2	11	7	14	25
60-69	5	8	7	11	19
70-79	2	5	7	8	13
80-89	1	2	5	6	8
90-99	0	0	1	1	1
TOTAL	12	51	40	77	128
Case fatality	24%	-	52%	-	-

MERS: Middle East respiratory syndrome.

[a] Five cases excluded due to missing age or sex data.

infection prevention measures in health facilities. It raises concerns about the 'superspreaders' as a source of extended transmission chains. The pandemic potential of MERS-CoV remains low. The basic reproduction number (R_0) is estimated at 0.69, lower than the R_0 for pre-pandemic SARS (0.80) and well below the epidemic threshold of 1 [28].

The significant proportion of caregivers likely infected in hospitals or at home played a role in transmission of MERS-CoV and is of concern. No secondary transmission has been associated with long-haul medical evacuation, suggesting that appropriate infection measures were applied and effective.

The fact that all but one of the primary cases in the known clusters are adult men originating from the Arabian Peninsula, suggests behavioural risk factors may play a role exposing them directly or indirectly to the reservoir of MERS-CoV. The severity of the diseases and fatal outcomes of the majority of the primary cases hinders effective exploration to identify risk factors.

Despite multiple efforts, no animal vectors or reservoirs have been identified as of yet with certainty. Exposure to camels has been reported for a few of the primary cases only.

The temporal distribution of cases suggests ongoing transmission of MERS-CoV on the Arabian Peninsula and the frequent appearance of nosocomial or familial clusters remains concerning. The number of new cases seems to have plateaued since April 2013.

Our data point towards a changing pattern of cases compared with the previously published case series [2-13] and with the review of the first 47 cases detected in SA [29]. More women and cases without comorbidities are being reported. The increased proportion of asymptomatic cases and the decreased CFR may reflect enhanced surveillance catching cases having remained unnoticed at the early stages of the epidemic.

Collaborative international efforts in the spirit of 'One health' are needed to identify the source of MERS-CoV and to describe the transmission paths into human populations on the Arabian Peninsula. With the Hajj, the Muslim pilgrimage to Mecca in Saudi Arabia, taking place in October this year and attracting 1.8 million foreign and 1.4 million domestic visitors, international public health efforts to mitigate and possibly contain this outbreak need to be reinforced. Continued vigilance in healthcare systems receiving severely ill patients with respiratory symptoms from the Arabian Peninsula is warranted.

Conflict of interest

None declared.

Authors' contributions

Pasi M.P. Penttinen, Kaja Kaasik-Aaslav, Alice Friaux, Alastair Donachie, Bertrand Sudre, Andrew J. Amato-Gauci, Ziad A. Memish and Denis Coulombier have all participated in the design of this study, data collection, data management, data analysis and writing the manuscript.

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High uptake of HPV immunisation in Scotland – perspectives on maximising uptake

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In September 2008, Scotland introduced a national human papillomavirus (HPV) immunisation programme with bivalent HPV vaccine, to prevent cervical cancer. This school-based programme routinely vaccinates girls aged between 12 and 13 years. A catch-up campaign, running over three years, also began at this time, offering vaccination to all girls aged 13 years to under 18 years old. The HPV immunisation campaign presented challenges due to this vaccine being targeted to girls in school and older girls who had left school. Following a long and comprehensive planning process, this campaign was successfully implemented across Scotland, delivering high vaccine uptake of 91.4% for three doses of vaccine in the first year (September 2008 to August 2009) for the routine cohort and 90.1% in the second year (September 2009 to August 2010) for the routine cohort. We describe the planning process, challenges and implementation strategies employed to achieve this high uptake.

Introduction

Genital infections with the human papillomavirus (HPV) are common, with most sexually active individuals expected to become infected with one or more HPV types in their lives [1]. Persistent infection of the cervix with oncogenic HPV types can cause cancer. HPV infection is implicated in more than 99% of cervical cancers [2]. Since 2000, around 320 new cases of cervical cancer are identified in Scotland every year [3]. Younger women are more likely to be diagnosed with cervical cancer: the highest incidence rate is for 35-40 year olds [3]. The burden of disease from cervical cancer has been reduced by two thirds since 1986 after a well-organised, quality assured cervical screening programme was implemented [4].

Of the 27 European Union Member States plus Norway and Iceland, 19 have introduced HPV immunisation into their vaccination schedule [19]. In June 2007, the United Kingdom (UK) Joint Committee on Vaccination and Immunisation (JCVI) [5] recommended to the UK Government Health Departments that vaccination against HPV should be introduced routinely for females aged 12-13 years [6]. This recommendation was supported by an independent cost-benefit analysis which indicated that an uptake for three doses of vaccine of 80% or more would be cost effective for this routine cohort providing that vaccine protection lasted for at least 10 years [7]. Modelling also informed a further recommendation that a catch-up campaign for all girls who were aged 13 to under 18 years at the start of the programme in September 2008 would also be cost effective [8].

In Scotland, responsibility for health and education are devolved to the national government. The country follows the UK immunisation schedule and benefits from UK-wide procurement of vaccine and national provision of standard guidance on immunisation practice (the Green Book) [9]. Scotland's 5.2 million population is divided into 14 regional health boards, which coordinate the local delivery of the national vaccination programme.

On the basis of the JCVI recommendation, in 2007, the Scottish Government announced plans for a routine programme for girls in second year of secondary school, aged 12-13 years [10] from September 2008 and a catch-up programme for girls aged 13-17 years to run over three years (September 2008 – August 2011) [11]. The average number of girls to be immunised annually as part of the routine programme is 25,500. For the catch-up campaign, the total target population of girls was around 77,000. While no specific target for uptake of HPV vaccination was set, the expectation was that uptake of 80% or more should be achieved for the routine programme. No figure was set for the catch-up campaign.

The proposed HPV programme had a high degree of political commitment, having featured in party manifestos in the Scottish Government elections in 2007. There was extensive media coverage of what was portrayed as the first 'anti-cancer' vaccine. This heightened from August 2008 when a British television celebrity announced her diagnosis with cervical cancer at the age of 27 and died in 2009 [12].

The Scottish Government asked Health Protection Scotland (part of National Service Scotland, with responsibility for public health) to ensure that there was a common approach to delivering the HPV immunisation programme across Scotland; that it was introduced to budget and on time; and to assess its uptake and consequent impact on health. This paper outlines the design and implementation of the HPV immunisation programme in Scotland, preliminary evaluation and the resulting uptake in the target population.

Methods

Project design and implementation

A number of decisions were made before planning could begin.

The optimum model of delivery

School-based delivery, delivery through primary care, or using a mixed model of both, were all considered. Following a subjective appraisal against key areas of implementation of the programme (including epidemiology and surveillance, service delivery, data management, communications and education criteria), an entirely school-based model, for those still at school was favoured. Health boards were left to decide how to best reach those who had left school (mainly aged over 16 years), choosing between delivery via general practice or specific health board run vaccination clinics.

Timing and phasing of the catch-up campaign

It was decided to start the catch-up at the same time or soon after the routine programme (1 October 2008) and spread the catch-up campaign over three years with oldest girls being immunised first. This entailed vaccination of 16-17 year olds in the first year (2008–09), 15-16 year olds in the second year (2009–10), with an option for anyone eligible for the catch-up to start and/or complete a vaccine course during the third year. The catch-up campaign ended in August 2011.

Identification of potentially 'hard-to-reach' girls and consideration of approaches through which they may be encouraged to participate in the campaign

'Hard-to reach' was defined as any combination of factors leading to a systematically increased likelihood of developing cervical cancer and/or reduced potential health gain from HPV immunisation, as a consequence of social or access issues in a defined group of people. These factors may result in: less likelihood of being immunised; less likelihood of attending for cervical screening; increased risk of persistent HPV infection. Approaches to enhance equitable access to the vaccine were developed.

Undertaking research to allow establishment of fit for purpose surveillance

Five key areas for specific study were identified.

- Identify knowledge and attitudes about HPV and cervical cancer and the proposed vaccine in parents, girls, education and healthcare professionals. Subsequent testing of the acceptability of proposed messages to be included in public information materials.
- Develop an inexpensive robust HPV assay which could be used for surveillance purposes to identify, measure and monitor HPV infection in age groups eligible for vaccination [13,14].
- Establish background prevalence and circulating genotypes of HPV in unimmunised populations before the vaccine programme commenced [15].
- Establish a surveillance system to monitor vaccine uptake, safety and early impact of vaccine through the effects on HPV prevalence in the population attending for cervical screening (from the age of 20).
- Identify the characteristics of those who do not attend for cervical screening against those who do attend for cervical screening [16], to inform if using samples from the cervical screening programme is representative of women in Scotland.

The timeline for implementation is shown in Figure 1. A formal project management approach was adopted with a Programme Manager put in place using Prince2 methodology to monitor work-stream activities and manage risk. Five work-streams were created to address key aspects of implementation. Members of these work-streams were drawn from public health professionals in Scotland, from within Health Protection Scotland, health boards, National Health Service supporting services (including data services and communications) and Scottish Government. Members of work-streams were not paid for participation. Generally, meetings for each work-stream were held monthly, but frequency varied depending on the stage of the programme. All work-streams had Scottish Government and Programme Manager representatives.

Service Delivery

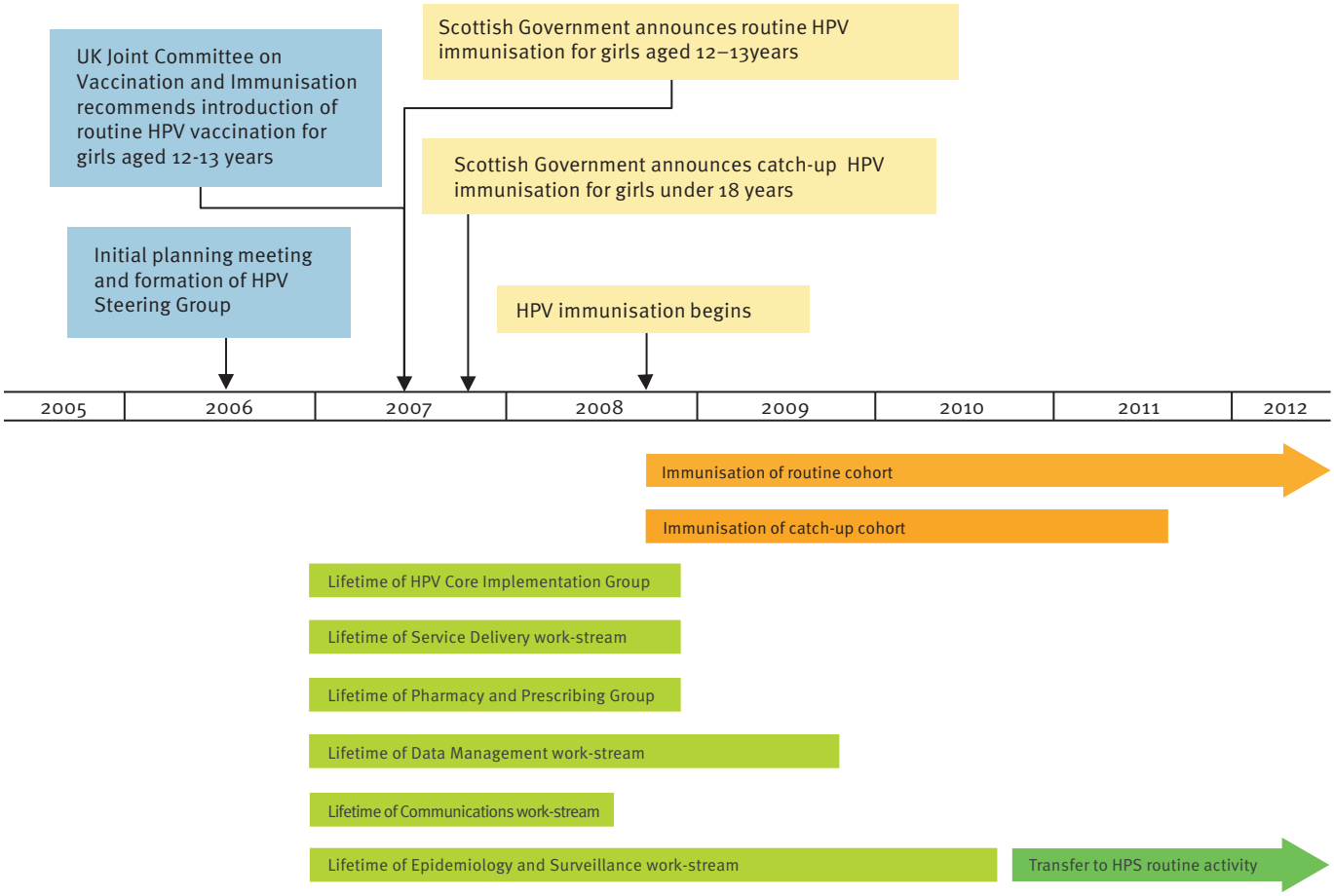
This work-stream ensured NHS preparedness by establishing good partnerships with health boards on local delivery, data flow and vaccine distribution. This work-stream undertook a performance management role by reviewing health board implementation plans and facilitating the sharing of good practice to ensure a consistency in access to the programme, especially for 'hard to reach' groups. This work-stream monitored service delivery in the initial stages. In addition, it also considered issues of consent. The Scottish Government led negotiations with primary care practitioners for enhanced services at a national level. Members included representatives from health boards, schools, education, school nurses, general practice, pharmacy and from all other work-streams. The chair was a senior public health clinician from one of the health boards.

Pharmacy and Prescribing

This working group, a sub-group of the Service Delivery work-stream, provided advice on pharmaceutical aspects and developed processes to: ensure the safe prescription (developed national patient group

Figure 1

Timeline for HPV immunisation programme planning and implementation in Scotland



HPS: Health Protection Scotland; HPV: human papillomavirus; UK: United Kingdom.

direction), supply and administration of vaccine; ensure vaccine procurement, storage and distribution complied with legislation and other requirements; ensure local systems for ordering, storing and distributing vaccine. This group also communicated progress through the Scottish Vaccine Update newsletter [17]. Members included pharmacy and logistics experts and representatives from health boards. The chair was a pharmacist from the National Health Service.

Data Management

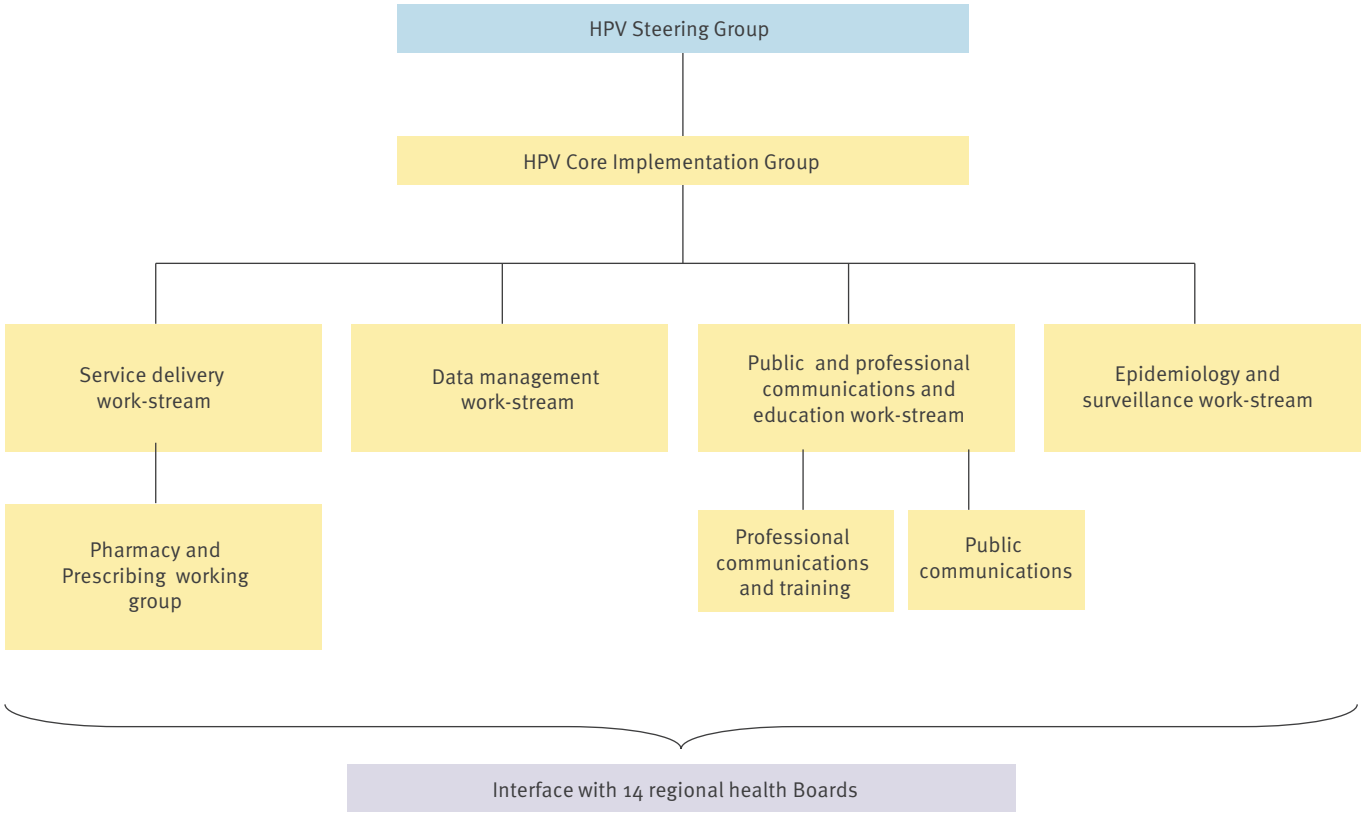
This work-stream identified the eligible cohort and put in place call and recall of girls according to the vaccine schedule and ensured the flow of data from the point at which a girl is called for vaccination, to recording when vaccination is given. This required modification of national information systems and provided data to calculate uptake rates. This work-stream also managed the interface between education and public health departments for girls who had left school. Members included experts on data systems, systems design, data analysis, epidemiologists and representatives from health boards, education, screening, general practice and other work-streams. The chair was a senior public health clinician from one of the health boards, who had a special interest in national data systems.

Communication and Education

This work-stream developed and implemented a multimedia campaign (including Internet, TV and cinema) to raise awareness, understanding and acceptance of the HPV immunisation among girls and their parents, healthcare and education professionals. Professional communications included briefing key stakeholders, informing service providers through regular professional letters, and training immunisers (i.e. nurses providing vaccination in schools). A common strapline for all materials 'Together we can beat cervical cancer' and a brand image based on a school girl talking to her friends were designed. Additional work was done to reach girls who had left school, including using

Figure 2

Programme structure for the HPV Immunisation Programme in Scotland



HPS: Health Protection Scotland; HPV: human papillomavirus

pink camper-vans to promote awareness. Members included public communications experts, training experts, epidemiologists and representatives from schools, education, general practice, national health telephone help-line (NHS24), health boards and other work-streams. The chair was a senior communications expert from the National Health Service.

Epidemiology and Surveillance

This work-stream put in place tools to evaluate the immunisation programme, in terms of uptake and safety, and to monitor the impact of the programme on rates of high-risk HPV infection, cervical cancer and on cancer precursors. The aim being that this would provide evidence to inform decisions about the future mix of screening, HPV testing and immunisation needed to continue to effectively prevent, detect and treat cervical cancer. A national Scottish HPV Reference Laboratory was established. Members of this work-stream included epidemiologists, data analysts, statisticians, laboratory representatives and representatives from the data management group, health boards and the Health Protection Agency in England (currently Public Health England) to ensure harmonisation of surveillance across the UK. This work-stream was chaired by the senior clinician and programme lead within Health Protection Scotland.

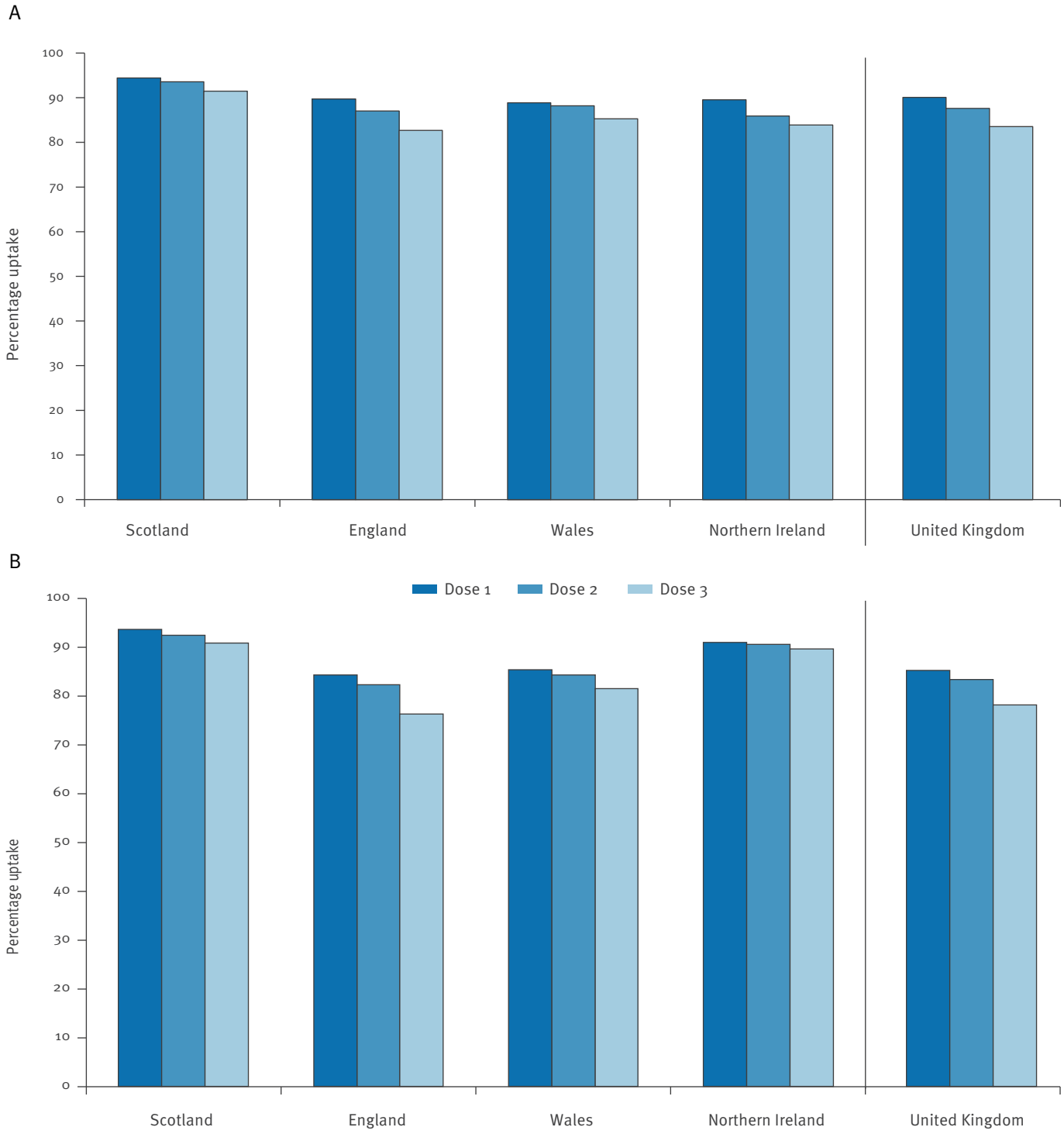
The progress of these work-streams was closely coordinated by a Core Implementation Group which met monthly (Figure 2). This group comprised the chairs of the work-streams, programme management and leads from the Scottish Government. A government appointed steering group oversaw the programme, signed off strategic decisions and commissioned reviews by external auditors, 'gateway reviews', to look in detail at risks, issues, governance and processes at key stages in the planning process. This group met quarterly, with membership drawn from senior staff involved with the programme including organisation directors, leads from schools, education, general practice, screening, sexual health and health boards and public/patient representation. The chair was a senior executive from one of the health boards, who was not directly involved in the programme.

Vaccine uptake

Scotland has well established universal healthcare data systems. Every citizen has a unique Community Health Index (CHI) number and medical data systems use this

Figure 3

HPV vaccine uptake in routine year (girls aged 12–13 years) for (A) 2008–09[a] and (B) 2009-10[b], United Kingdom



HPV: human papillomavirus.

Adjustments to the denominator populations used to calculate these uptake statistics are ongoing and rates shown here should be regarded as indicative; final uptake data will be published by each UK administration separately.

[a] First year of the programme.

[b] Second year of the programme.

Source: Information Services Division, NHS National Services Scotland; Public Health Wales; for England and Northern Ireland data were provided via personal communication Joanne White, September 2010, Department of Health (Health Protection Agency) and Ruth Campbell, September 2010, Public Health Agency in Northern Ireland.

Table 1

Uptake of HPV vaccine for the first routine school year (12–13 year old girls), Scotland, 2008–09

NHS Board	Number of girls in cohort	Number 1st dose	% uptake of 1st dose	Number 2nd dose	% uptake of 2nd dose	Number 3rd dose	% uptake of 3rd dose
Ayrshire and Arran	2,091	1,968	94.1	1,957	93.6	1,943	92.9
Borders	653	616	94.3	610	93.4	604	92.5
Dumfries and Galloway	867	835	96.3	833	96.1	826	95.3
Fife	2,026	1,891	93.3	1,876	92.6	1,835	90.6
Forth Valley	1,703	1,630	95.7	1,618	95.0	1,582	92.9
Grampian	2,964	2,802	94.5	2,778	93.7	2,718	91.7
Greater Glasgow & Clyde	6,564	6,177	94.1	6,120	93.2	5,982	91.1
Highland	1,786	1,661	93.0	1,648	92.3	1,622	90.8
Lanarkshire	3,465	3,306	95.4	3,266	94.3	3,118	90.0
Lothian	4,373	4,114	94.1	4,074	93.2	4,003	91.5
Orkney	117	108	92.3	107	91.5	106	90.6
Shetland	132	124	93.9	124	93.9	123	93.2
Tayside	2,297	2,190	95.3	2,164	94.2	2,098	91.3
Western Isles	171	158	92.4	157	91.8	150	87.7
All Scotland	**29,286**	**27,652**	**94.4**	**27,403**	**93.6**	**26,781**	**91.4**

to ensure accurate record keeping and population registers for preventive medical services. The Scottish Child Health Surveillance Programme – Schools system [30] was used as the call and recall register for school-based immunisation. Health boards, education authorities and private schools worked together to revise the accuracy and completeness of their data prior to the initial call.

Eligible girls who were not at school were identified by extracting data from school registers of those who had left school. Individual records of those immunised were sent to central data collection points in the individual health boards and entered into the child health system. Details of vaccination status were extracted from the system, collated, analysed and presented using validated national procedures. Uptake rates were calculated using population denominators derived from the system.

Preliminary evaluation

A qualitative evaluation was undertaken following the end of the first year of vaccination. The aim of this survey was to establish how the programme structure and management had functioned and how the performance management aspects had worked. The questions were based on previous surveys of projects related to immunisation, modified through consultation and adapted into an online format for ease of completion and analysis.

The survey was made available for completion to representatives of all health board immunisation teams and all members of the Core Implementation Group, the National Steering Group and the work-streams. Work-streams contributed composite answers, but individuals may also have returned a completed survey. Not all questions were relevant to all respondents. Common elements and themes were manually identified across the range of responses by a member of Health Protection Scotland staff who was not involved in the programme.

Results

Programme

The planning process was effective and immunisation began on time as planned. This was the first time there had been performance management of health boards for a national campaign. There was equal and consistent participation from all health boards.

The programme was audited twice during the planning process at 'gateway reviews'. At these reviews, external auditors scrutinised processes, governance, risks and issues. In addition to reviewing documentation, interviews were held with key personnel in the programme. Financial impact was assessed at each review. The programme received positive evaluation at each review and was allowed to proceed onto the next stage.

The HPV Steering Group met for the last time in September 2010, when the success of the planning process and implementation was acknowledged and the programme officially closed. Immunisation continues

for the routine cohort as part of the routine childhood programme. Long term monitoring of HPV immunisation and the impact on disease continues. These responsibilities lie with Health Protection Scotland.

Vaccine uptake

Vaccine uptake in the routine cohort (girls aged 12–13 years)

Figure 3 shows uptake data for the first year of the vaccination campaign (2008–09), comparing uptake of first, second and third doses for all UK countries. The Scottish programme achieved 91.4% uptake for all three doses of vaccine, compared with 83.5% for the average across the whole of the UK. Scotland continued this success in year 2 of the vaccination campaign (2009–10), with 90.1% uptake in the routine cohort.

Table 1 shows vaccine uptake for the routine cohort by health boards in 2008–09. All health board regions achieved uptake of more than 87% for three doses of vaccine in this year. Health board regions encompass inner city, rural and island regions.

Vaccine uptake in the catch-up campaign

Vaccine uptake for those girls in the catch-up cohort and still attending school was comparable to uptake of the routine year, at overall 87% uptake of three doses for all school years [18]. Vaccine uptake for those girls who had left school was significantly lower at 32% uptake of three doses of vaccine. Overall, the uptake of three doses of vaccine for all girls eligible (both in and out of school) was 65% uptake of three doses of vaccine.

A more detailed analysis of routine and catch-up uptake has been published elsewhere, including the effect of deprivation on uptake [31].

Qualitative evaluation

Thirty responses were received to the online survey. These were individual responses and group responses, which limited any detailed analysis. Responders provided satisfaction scores to key questions about each work-stream, these are summarised in Table 2. Highest levels of satisfaction (scoring over 90% for what worked well) were for:

- the logistics of vaccine supply, distribution and dispensing;
- in-school vaccination arrangements and identification of girls in school;
- consent procedures (development of consent form and process of obtaining consent);
- communication resources for girls, partnership working and media campaign (this media campaign was award winning);
- input from Health Protection Scotland;
- expert advice and guidance managing adverse events and associated communications;
- data security and information governance;
- direction given by the National Steering Group.

Lowest levels of satisfaction (scoring less than 70%) were for:

- out of school vaccination arrangements and the identification of girls out of school;
- data flow between health boards and education authorities;
- capturing data across health board boundaries.

Discussion

Immunisation programmes constitute an essential method of protecting health. A programme is composed of a number of inter-linked resources, processes and structures which require co-ordination to enhance overall effectiveness and efficiency. To introduce HPV immunisation in Scotland, a project management approach was adopted to achieve these ends. This report discusses the relationship between the high uptake attained and key themes identified from this structured approach.

The key measure of initial effectiveness, achieving at least 80% uptake of completed courses in the cohort eligible for routine immunisation was attained. Coverage was lower in the cohorts eligible for the catch-up campaign but still reached 65% overall for three doses of vaccine. There was however a considerable disparity between uptake in those in and out of school who were eligible for the catch-up campaign. The reasons for this have been explored elsewhere [31].

The uptake rate for completed courses of HPV immunisation in the routine cohort in Scotland (91% in the first year of implementation) is amongst the highest reported in the world. Uptake in comparably resource-rich countries within Europe [19] ranged between 24-84%, was 14% in the United States [20] and 73% in Australia [21]. Uptake in those countries delivering vaccine only in schools ranged between 63 and 83%. In many countries, uptake is lower than expected. Scotland also achieves high uptake rates for other immunisations: completion of childhood primary course at the age of one year is currently 97.4%; the first dose of measles-mumps-rubella (MMR) vaccine at the age of two years is currently 94.3%; completion of booster courses is currently 91.9% at the age of five years [22]. This indicates a general population acceptance for immunisation as a measure to protect personal and family health. It is also a sign that the country's well-established public health and primary care systems are effective.

Based on structured feedback from participants, the introduction of the HPV immunisation programme was perceived to have been effectively managed. This was despite challenges in the initial planning phase, a lack of national agreement with primary care practitioners for the first time for a new vaccine programme, introduction of new data systems in some health board areas and the need to schedule a multi-dose course for the first time in an adolescent age group.

Table 2

Qualitative evaluation of the HPV immunisation programme, results of the online survey, components rated as having worked well, Scotland, 2010

Work stream	Assessed components	Positive responses / Total responses
Service delivery	Operational service delivery (e.g. infrastructure, resources, contracts)	21 / 25
	In-school vaccination arrangements	27 / 27
	Out of school vaccination arrangements	15 / 24
	Partnership working (e.g. education authorities, religious groups)	25 / 26
	Consent procedures	23 / 24
	Expert advice and guidance	23 / 24
Data management	Identification of population of girls in school	25 / 26
	Identification of population of girls out of school	16 / 25
	Data flow between health and education authorities	17 / 26
	Data security and information governance	19 / 20
	Capturing data across Health Board boundaries	8 / 13
	Data extraction, transfer and analysis	9 / 12
Procurement and logistics	National vaccine selection and procurement process	13 / 18
	Vaccine supply and delivery to Health Boards	17 / 18
	Liaison with Holding Centres	18 / 18
	Resources/capacity for vaccine storage	19 / 19
	Cold chain maintenance	20 / 20
	Patient Group Directives (communal prescriptions)	20 / 20
Public and service communication	Training resources for healthcare professionals and providers	18 / 22
	Communication with healthcare professionals	22 / 25
	National HPV vaccination media campaign	24 / 26
	Expert advice and support for communication	23 / 25
	Communication resources for girls receiving the vaccine (e.g. leaflets, websites)	23 / 25
Epidemiology and surveillance	Monitoring of vaccine uptake	20 / 24
	Vaccine safety monitoring	22 / 24
	Advice and guidance for managing adverse events	22 / 24
	Long-term monitoring of vaccine impact on cervical cancer and cancer precursors	9 / 12
National project management	Relationship between national programme and local immunisation coordinators	16 / 20
	Direction given by HPV National Steering Group	20 / 21
	Input into the campaign from HPS	22 / 24
	Involvement of faith groups in planning stages	7 / 9
	Programme governance (e.g. reporting, accountability)	15 / 18

The project management approach adopted is unlikely to be of itself a key factor in the achievement of the relatively high uptake rate. However, it allowed the identification of some of the key factors that may have influenced uptake rates and has highlighted areas for improvement. Three broad groups of inter-related factors were identified by those involved in managing the project as key to the achievement of the high levels of uptake: school-based delivery, tailored communications directed at adolescent girls and good logistical services.

High rates of uptake of completed courses of HPV vaccination achieved through school-based models of delivery have been reported in other countries. The differential in rates between girls in and out of school has been noted in the UK previously with the meningococcal sero-group C conjugate vaccination catch-up campaign [23]. The positive experience of UK school nurses involved in the programme and the motivation this gave them has been reported [24].

The importance of targeted communications is clearly reflected in the uptake rates. According to information received from the Communications work-stream based on their work to evaluate the communications produced, girls, parents and healthcare professions were satisfied with the information they received. The high

profile illness and death of a young television celebrity from cervical cancer could have played a role in the uptake of the vaccine. The year in which she was ill and died (2008–09) saw a large increase in the number of young women in Scotland attending cervical screening [25].

The National Institute for Clinical Excellence (NICE) guidance [26] and Cochrane reviews [27,28] advocate the use of data systems for call-recall, and in this case existing registers could be adapted relatively easily for this purpose, although significant work was needed to establish accuracy within the system. A draw back to the catch-up campaign was the lack of an accurate register of those older girls who were not at school.

There were a number of limitations with the approach taken. Health board registers of 16 and 17 year old girls who had left school were inaccurate and uptake rates based on them are therefore estimates. Survey responses were subjective and not collected uniformly (some from individuals, some via group discussion) - this is therefore a qualitative unstructured assessment. Scottish Government invested, in relative terms, a considerable resource in ensuring the successful planning and implementation of the programme. Scotland is a small, relatively ethnically homogenous country (although there is considerable socio-economic inequality). These factors may limit the application of these findings to other programmes and settings. However, we believe that this approach could act as a general framework for the implementation of new immunisation programmes in other European countries

Conclusion

We conclude that a structured, managed approach to preparation for delivery of new immunisation programmes is essential in achieving high and inclusive uptake. This structured approach allowed for transparency of process, accountability for decision making and provided a process that could be reviewed at key stages..

Introduction of the HPV immunisation programme in Scotland was successful in achieving high uptake. This success was sustained in year 2, despite coincident with the influenza A(H1N1)pdm09 pandemic and implementation of the influenza A(H1N1)pdm09 vaccination programme – which fell between doses one and two of the schedule.

Further analyses and discussion on HPV uptake rates within Scotland are in preparation. The HPV immunisation campaign continues in Scotland for girls aged 12–13 years. Our current surveillance work focuses on identifying the effects of vaccination on HPV infections identified through attendance at first cervical screening appointment. In Scotland, cervical screening currently begins at age 20 years, and in 2012 we estimate around 70% of girls attending screening at age 20 will have received three doses of HPV vaccine [29].

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Conflict of interest

None declared.

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